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chapter 11

Respiratory System

I. UPPER RESPIRATORY SYSTEM

The upper respiratory system consists of the **nose, nasopharynx,** and **oropharynx.**

II. LOWER RESPIRATORY SYSTEM (FIGURE 11.1)

The lower respiratory system consists of the **larynx, trachea, bronchi,** and **lungs.** The first sign of development is the formation of the **respiratory diverticulum** in the ventral wall of the primitive foregut during week 4. The distal end of the respiratory diverticulum enlarges to form the **lung bud.** The lung bud divides into two **bronchial buds** that branch into the **main (primary), lobar (secondary), segmental (tertiary),** and **subsegmental bronchi.** The respiratory diverticulum initially is in open communication with the foregut, but eventually they become separated by indentations of mesoderm, the **tracheoesophageal folds.** When the tracheoesophageal folds fuse in the midline to form the **tracheoesophageal septum,** the foregut is divided into the trachea ventrally and esophagus dorsally.

A. Development of the larynx. The opening of the respiratory diverticulum into the foregut becomes the **laryngeal orifice.** The laryngeal epithelium and glands are derived from endoderm. The laryngeal muscles are derived from somitomeric mesoderm of pharyngeal arches 4 and 6 and therefore are innervated by branches of the vagus nerve (cranial nerve [CN] X); i.e., the superior laryngeal nerve and recurrent laryngeal nerve, respectively. The laryngeal cartilages (thyroid, cricoid, arytenoid, corniculate, and cuneiform) are derived from somitomeric mesoderm of pharyngeal arches 4 and 6.

B. Development of the trachea

1. **Sources.** The tracheal epithelium and glands are derived from endoderm. The tracheal smooth muscle, connective tissue, and C-shaped cartilage rings are derived from visceral mesoderm.
2. **Clinical consideration. Tracheoesophageal fistula** is an abnormal communication between the trachea and esophagus that results from improper division of foregut by the tracheoesophageal septum. It is generally associated with **esophageal atresia** and **polyhydramnios.** Clinical features include excessive accumulation of saliva or mucus in the nose and mouth; episodes of gagging and cyanosis after swallowing milk; abdominal distention after crying; and reflux of gastric contents into lungs, causing pneumonitis. Diagnostic features include inability to pass a catheter into the stomach and radiographs demonstrating air in the infant's stomach. There are five different anatomical types of esophagus and trachea malformations as follows:

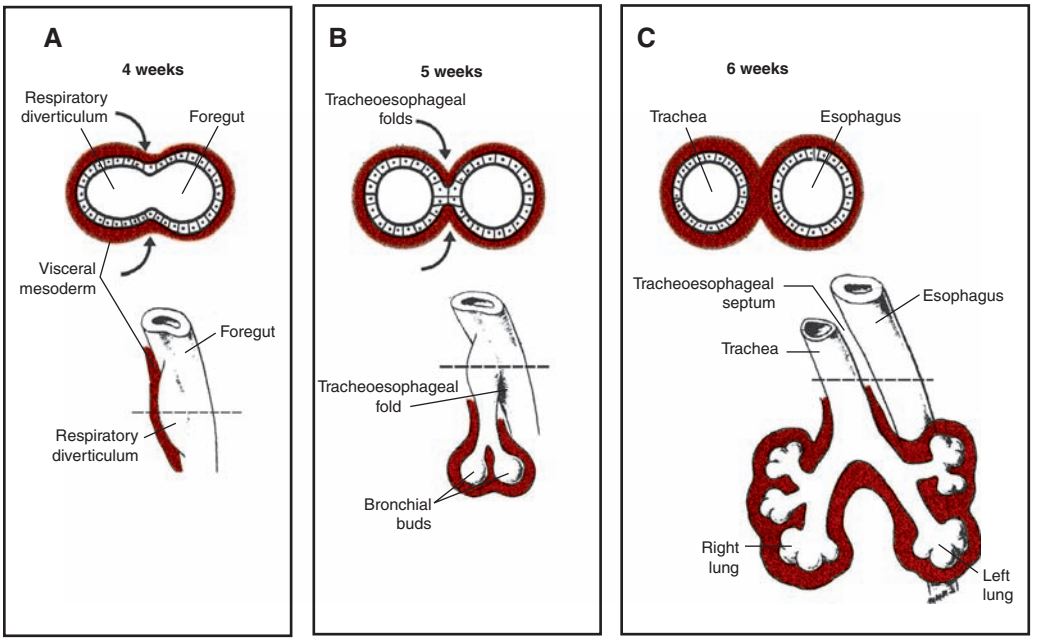
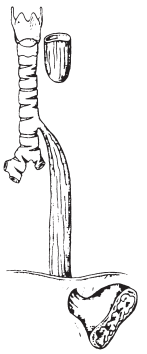


FIGURE 11.1. Development of respiratory system at **(A)** 4 weeks, **(B)** 5 weeks, and **(C)** 6 weeks. Both lateral views and cross-sectional views are shown. Note the relationship of the respiratory diverticulum and foregut. *Curved arrows* indicate the movement of the tracheoesophageal folds as the tracheoesophageal septum forms between the trachea and esophagus.

a. **Esophageal atresia with a tracheoesophageal fistula at the distal one-third end of the trachea (Figure 11.2).** This is the most common type, occurring in 82% of cases. The anteroposterior (AP) radiograph in Figure 11.2 of this malformation shows an enteric tube (*arrow*) coiled in the upper esophageal pouch. The air in the bowel indicates a distal tracheoesophageal fistula.



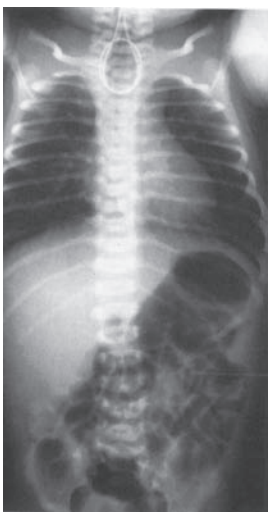


FIGURE 11.2. Esophageal atresia with a tracheoesophageal fistula at the distal one-third end of the trachea.

b. Esophageal atresia only (Figure 11.3). This malformation occurs in 9% of cases.

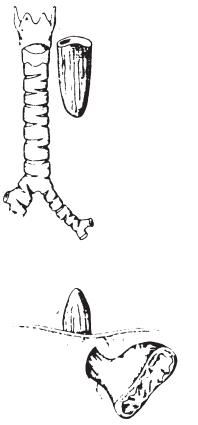


FIGURE 11.3. Esophageal atresia.

c. H-type tracheoesophageal fistula only (Figure 11.4). This malformation occurs in 6% of cases. The barium swallow radiograph in Figure 11.4 shows a normal esophagus (E), but dye has spilled into the trachea (T) through the fistula and outlines the upper trachea and larynx.

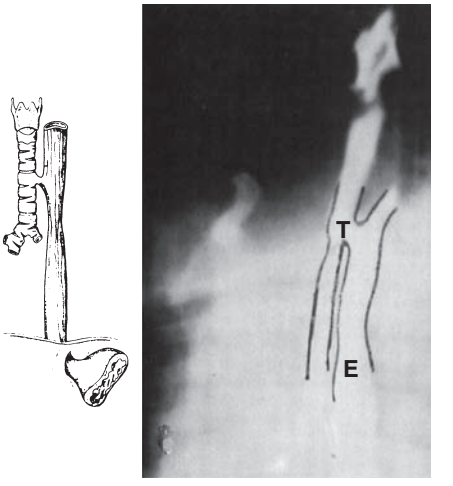


FIGURE 11.4. H-type tracheoesophageal fistula.

d. Esophageal atresia with a tracheoesophageal fistula at both proximal and distal ends (Figure 11.5). This malformation occurs in 2% of cases.

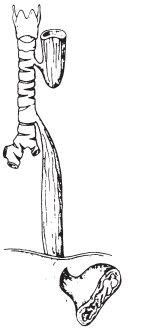


FIGURE 11.5. Esophageal atresia with a tracheoesophageal fistula at both proximal and distal ends.

e. Esophageal atresia with a tracheoesophageal fistula at the proximal end (Figure 11.6). This malformation occurs in 1% of cases.

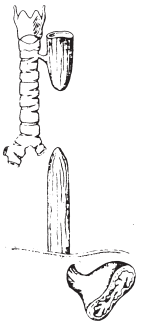


FIGURE 11.6. Esophageal atresia with a tracheoesophageal fistula at the proximal end.

C. Development of the bronchi (Figure 11.7)

1. Stages of development

a. The lung bud divides into two **bronchial buds.**

b. In week 5 of development, bronchial buds enlarge to form **main (primary) bronchi.**

c. The right main bronchus is larger and more vertical than the left main bronchus; this relationship persists throughout adult life and accounts for the greater likelihood of foreign bodies lodging on the right side than on the left.

d. The main bronchi further subdivide into **lobar (secondary) bronchi** (three on the right side and two on the left side, corresponding to the lobes of the adult lung).

e. The lobar bronchi further subdivide into **segmental (tertiary) bronchi** (10 on the right side and 9 on the left side), which further subdivide into **subsegmental bronchi.**

f. The segmental bronchi are the primordia of the **bronchopulmonary segments,** which are morphologically and functionally separate respiratory units of the lung.

g. As the bronchi develop, they expand laterally and caudally into a space known as the primitive pleural cavity.

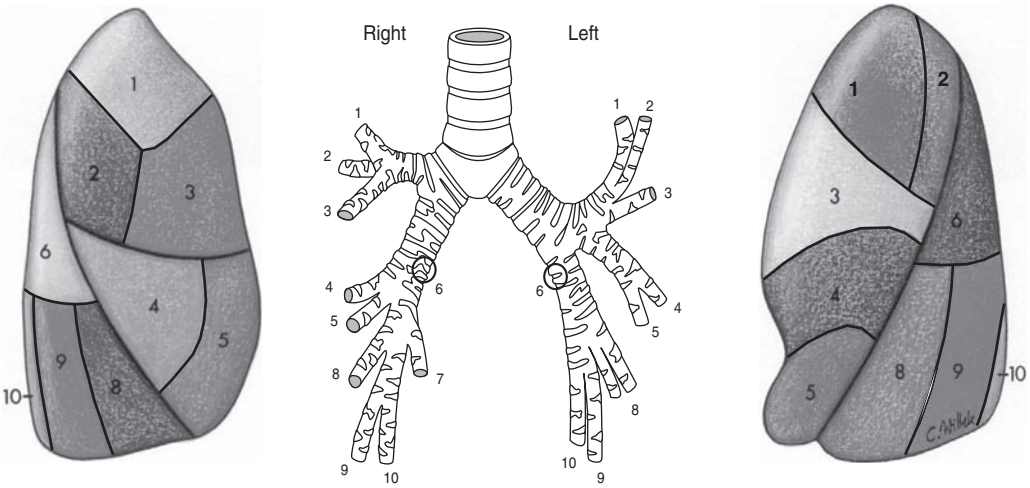


FIGURE 11.7. Distribution of bronchopulmonary segments and their relationship to the tracheobronchial tree. Segmental bronchi of the right and left lungs are numbered. Right lung: 1, 2, 3 = segmental bronchi that branch from the upper lobar bronchus; 4, 5 = segmental bronchi that branch from the middle lobar bronchus; 6, 7, 8, 9, 10: segmental bronchi that branch from the lower lobar bronchus. Note that bronchopulmonary segment 7 is not represented on the outer costal surface of the right lung (7 is located on the inner mediastinal surface). Left lung: 1+2, 3, 4, 5: segmental bronchi that branch from the upper lobar bronchus; 6, 8, 9, 10: segmental bronchi that branch from the lower lobar bronchus. Note that there is number 7 segmental bronchus associated with the left lung.

h. The visceral mesoderm covering the outside of the bronchi develops into **visceral pleura,** and somatic mesoderm covering the inside of the body wall develops into **parietal pleura.**

i. The space between the visceral and parietal pleura is called the **pleural cavity.**

2. **Sources.** The bronchial epithelium and glands are derived from endoderm. The bronchial smooth muscle, connective tissue, and cartilage are derived from visceral mesoderm.

3. **Clinical considerations**

a. **Bronchopulmonary segment** is a segment of lung tissue supplied by a segmental (tertiary) bronchus. Surgeons can resect diseased lung tissue along bronchopulmonary segments rather than remove the entire lobe.

b. **Congenital lobar emphysema (CLE; Figure 11.8)** is characterized by progressive overdistention of one or the upper lobes or the right middle lobe with **air.** The term "emphysema" is a misnomer because there is no destruction of the alveolar walls. Although the exact etiology remains unknown, many cases involve **collapsed bronchi** due to **failure of bronchial cartilage formation.** In this situation, air can be inspired through collapsed bronchi but cannot be expired. During the first few days of life, fluid may be trapped in the involved lobe, producing an opaque, enlarged hemithorax. Later, the fluid is resorbed, and the classic radiological appearance of an emphysematous lobe with generalized radiolucency (hyperlucent) is apparent. The expiratory AP radiograph in Figure 11.8 shows a hyperlucent area in the emphysematous right upper lobe due to air trapping.

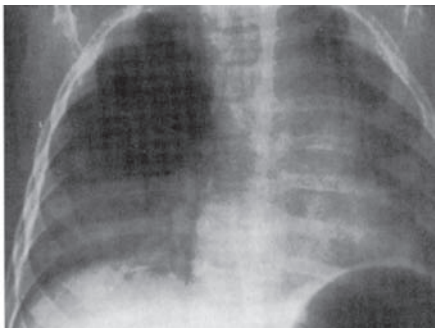


FIGURE 11.8. Congenital lobar emphysema.

c. **Congenital bronchogenic cysts (Figure 11.9)** represent an abnormality in bronchial branching and may be found within the mediastinum (most commonly) or intrapulmonary. Intrapulmonary cysts are round, solitary, sharply marginated, and **fluid filled** and do not initially communicate with the tracheobronchial tree. Because intrapulmonary bronchogenic cysts contain fluid, they appear as water-density masses on chest radiographs. These cysts may become air filled as a result of infection or instrumentation. The AP radiograph in Figure 11.9 shows a large opaque area in the right upper lobe due to a fluid-filled cyst.

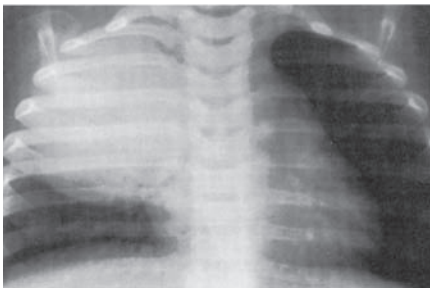


FIGURE 11.9. Congenital bronchogenic cyst.

d. **Bronchiectasis** is the abnormal, permanent dilatation of bronchi due to chronic necrotizing infection (e.g., *Staphylococcus*, *Streptococcus*, *Haemophilus influenzae*), bronchial obstruction (e.g., foreign body, mucous plugs, or tumors), or congenital conditions (e.g., Kartagener syndrome, cystic fibrosis, immunodeficiency disorders).

The lower lobes of the lung are predominately affected, and the affected bronchi have a saccular appearance. Clinical signs include cough, fever, and expectoration of large amounts of foul-smelling purulent sputum. Bronchiectasis may also be classified to a group of disorders known as chronic obstructive pulmonary disease (COPD), which are characterized by increased resistance to airflow during both inspiration and expiration due to airway obstruction. Other members of COPD include emphysema, chronic bronchitis, and asthma.

E. Development of the lungs

1. **Periods of development.** The lung matures in a proximal–distal direction, beginning with the largest bronchi and proceeding outward. As a result, lung development is heterogeneous; proximal pulmonary tissue will be in a more advanced period of development than distal pulmonary tissue.

   a. **Pseudoglandular period (weeks 7–16; Figure 11.10).** During this period, the developing lung resembles an exocrine gland. The numerous **endodermal tubules (ETs)** are lined by **simple columnar epithelium** and are surrounded by mesoderm containing a **modest capillary network.** Each endodermal tubule branches into 15–25 **terminal bronchioles (TBs).** During this period, respiration is not possible, and premature infants cannot survive. The diagram in Figure 11.10 shows the lung in the pseudoglandular period.

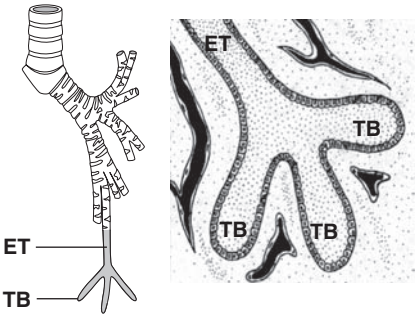


FIGURE 11.10. Pseudoglandular period.

   b. **Canalicular period (weeks 16–24; Figure 11.11).** During this period, the TBs branch into three or more **respiratory bronchioles (RBs).** The respiratory bronchioles subsequently branch into three to six **alveolar ducts (ADs).** The terminal bronchioles, respiratory bronchioles, and alveolar ducts are now lined by a **simple cuboidal epithelium** and are surrounded by mesoderm containing a **prominent capillary network.** Premature infants born before week 20 rarely survive. The diagram in Figure 11.11 shows the lung in the canalicular period.

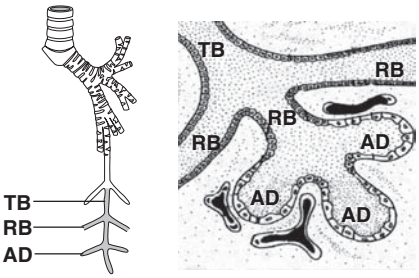


FIGURE 11.11. Canalicular period.

   c. **Terminal sac period (week 24 to birth; Figure 11.12).** During this period, **terminal sacs (TSs)** bud off the ADs and then dilate and expand into the surrounding mesoderm. The terminal sacs are separated from each other by **primary septae.** The simple cuboidal epithelium within the terminal sacs differentiates into **type I pneumocytes** (thin, flat cells that make up part of the blood–air barrier) and **type II pneumocytes** (which produce surfactant). The terminal sacs are surrounded by mesoderm containing a **rapidly proliferating capillary network.** The capillaries make intimate contact with the terminal sacs and thereby establish a **blood–air barrier** with

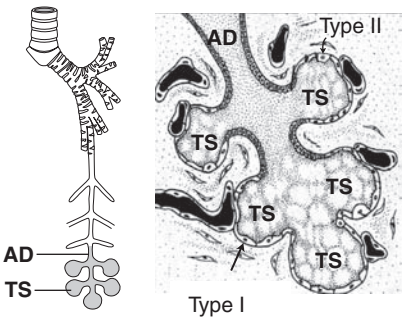


FIGURE 11.12. Terminal sac period.

the type I pneumocytes. **Premature infants born between week 25 and week 28 can survive with intensive care.** Adequate vascularization and surfactant levels are the most important factors for the survival of premature infants. The diagram in Figure 11.12 shows the lung in the terminal sac period.

d. **Alveolar period (week 32–age 8 years; Figure 11.13).** During this period, terminal sacs are partitioned by **secondary septae** to form adult **alveoli.** About 20–70 million alveoli are present at birth. About 300–400 million alveoli are present by 8 years of age. The major mechanism for the increase in the number of alveoli is formation of secondary septae that partition existing alveoli. After birth, the increase in the size of the lung is due to an **increase in the number of respiratory bronchioles.** On chest radiographs, lungs of a newborn infant are denser than an adult lung because of the fewer number of mature alveoli.

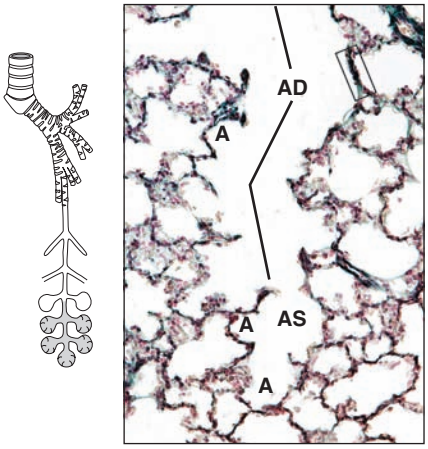


FIGURE 11.13. Alveolar period. A = adult alveoli; AD = alveolar duct; AS = alveolar sac.

2. **Clinical considerations**

a. **Aeration at birth** is the replacement of lung liquid with air in the newborn's lungs. In the fetal state, the functional residual capacity (FRC) of the lung is filled with liquid secreted by fetal lung epithelium via Cl^- transport using CFTR (cystic fibrosis transmembrane protein). At birth, lung liquid is eliminated by a reduction in lung liquid secretion via Na^+ transport by type II pneumocytes and resorption into pulmonary capillaries (major route) and lymphatics (minor route). Lungs of a stillborn baby will sink when placed in water because they contain fluid rather than air.

b. **Respiratory distress syndrome (RDS; Figure 11.14).**

i. RDS is caused by a deficiency or absence of **surfactant** that is produced by **type II pneumocytes.**

ii. This surface active agent is composed of **cholesterol** (50%), **dipalmitoylphosphatidylcholine** (DPPC; 40%), and **surfactant proteins A, B, and C** (10%) and coats the inside of alveoli to maintain alveolar patency.

iii. RDS is prevalent in premature infants (accounts for 50%–70% of deaths in premature infants), infants of diabetic mothers, infants who experienced fetal asphyxia or maternofetal hemorrhage (damages type II pneumocytes), and multiple-birth infants.

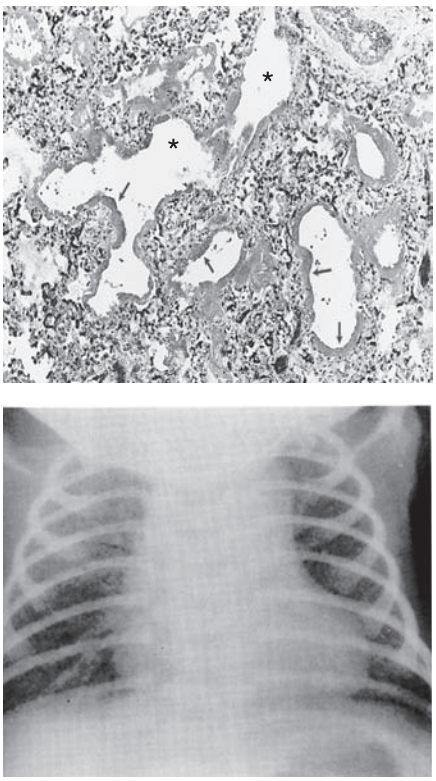


FIGURE 11.14. Respiratory distress syndrome (RDS).

iv. Clinical signs include dyspnea, tachypnea, inspiratory retractions of chest wall, expiratory grunting, cyanosis, and nasal flaring.
v. Treatments include administration of betamethasone (a corticosteroid) to the mother for several days before delivery (i.e., antenatal) to increase surfactant production, postnatal administration of an artificial surfactant solution, and postnatal high-frequency ventilation.
vi. RDS in premature infants cannot be discussed without mentioning **germinal matrix hemorrhage (GMS).** The germinal matrix is the site of proliferation of neuronal and glial precursors in the developing brain that is located above the caudate nucleus, in the floor of the lateral ventricles, and the caudal–thalamic groove. The germinal matrix also contains a rich network of fragile, thin-walled blood vessels.
vii. The brain of the premature infant lacks the ability to autoregulate the cerebral blood pressure.
viii. Consequently, increased arterial blood pressure in these blood vessels leads to rupture and hemorrhage into the germinal matrix. This leads to significant neurological sequelae, including cerebral palsy, mental retardation, and seizures.
ix. Antenatal corticosteroid administration has a clear role in reducing the incidence of GMH is premature infants.
x. The light micrograph in Figure 11.14 shows the pathological hallmarks of RDS, which are acinar atelectasis (i.e., collapse of the respiratory acinus, which includes the respiratory bronchioles, alveolar ducts, and alveoli), dilation of terminal bronchioles (shown by the asterisk), and deposition of an eosinophilic hyaline membrane material (*arrows*) that consists of fibrin and necrotic cells.
xi. The AP radiograph in Figure 11.14 shows the radiological hallmarks of RDS, which are a bell-shaped thorax due to under-aeration and reticulogranularity of the lungs caused by acinar atelectasis.

c. **Pulmonary agenesis** is the complete absence of a lung or a lobe and its bronchi. This is a rare condition caused by failure of bronchial buds to develop. Unilateral pulmonary agenesis is compatible with life.
d. **Pulmonary aplasia** is the absence of lung tissue but the presence of a rudimentary bronchus.
e. **Pulmonary hypoplasia (PH)** is a poorly developed bronchial tree with abnormal histology. PH classically involves the right lung in association with right-sided obstructive congenital heart defects. PH can also be found in association with **congenital diaphragmatic hernia** (i.e., herniation of abdominal contents into the thorax), which compresses the developing lung. PH can also be found in association with **bilateral renal agenesis or Potter's syndrome,** which causes an insufficient amount of amniotic fluid (oligohydramnios) to be produced, which in turn increases pressure on the fetal thorax.
f. **Cystic fibrosis (CF)** is an autosomal recessive genetic disorder caused by >1000 mutations in the **CFTR gene** on **chromosome 7q31.2** for the **cystic fibrosis transmembrane conductance regulator,** which functions as a chloride ion (Cl^-) channel. CF is most commonly (approximately 70% of cases in the North American population) caused by a **three–base pair deletion** at the site that codes for the amino acid **phenylalanine** at **position 508** (hence the mutation is called delta F508) of CFTR, such that phenylalanine is missing from the CFTR. However, there are a large number of deletions that can cause CF, and parents of an affected child can carry different deletions of CFTR. These mutations result in absent/near-absent CFTR synthesis, a block in CFTR regulation, or a destruction of Cl^- transport. Clinical features include production of abnormally thick mucus by epithelial cells lining the respiratory tract, resulting in obstruction of pulmonary airways, recurrent respiratory bacterial infections, and end-stage lung disease; pancreatic insufficiency with malabsorption; acute salt depletion; and chronic metabolic alkalosis. Males are almost always sterile due to the obstruction or absence of the vas deferens. Whites are the most commonly affected ethnic group, with CF occurring in 1 of 2500 live births.

Study Questions for Chapter 11

1. A young mother brings her recently born infant into your office and complains that the infant gags and chokes after swallowing milk. A physical examination indicates excessive saliva and mucus around the mouth and nose, abdominal distention, pneumonitis, and radiographs indicate air in the infant's stomach. What is the most likely cause?

(A) Hypertrophic pyloric stenosis
(B) Tracheoesophageal fistula
(C) Congenital lobar emphysema
(D) Respiratory distress syndrome
(E) Pulmonary hypoplasia

2. Within hours after birth, a baby whose mother is diabetic had a rising respiratory rate and labored breathing. The baby became cyanotic and died. Postmortem histological examination revealed collapsed alveoli lined with eosinophilic material. What is the diagnosis?

(A) Congenital emphysema
(B) Respiratory distress syndrome
(C) Cystic fibrosis
(D) Tracheoesophageal fistula
(E) Pulmonary carcinoma

3. The trachea is lined with pseudostratified ciliated columnar epithelium with goblet cells. This epithelium is derived from

(A) neuroectoderm
(B) endoderm
(C) ectoderm
(D) visceral mesoderm
(E) mesoderm of fourth and sixth pharyngeal arches

4. Smooth muscle, connective tissue, and cartilage of primary bronchi are derived from which of the following sources?

(A) Neuroectoderm
(B) Endoderm
(C) Ectoderm
(D) Visceral mesoderm
(E) Mesoderm of pharyngeal arches 4 and 6

5. Components of the blood–air barrier in the lung are derived from which of the following sources?

(A) Ectoderm only
(B) Visceral mesoderm only
(C) Visceral mesoderm and ectoderm
(D) Endoderm and ectoderm
(E) Visceral mesoderm and endoderm

6. The respiratory diverticulum initially is in open communication with the primitive foregut. Which of the following embryonic structures is responsible for separating these two structures?

(A) Laryngotracheal groove
(B) Posterior esophageal folds
(C) Laryngotracheal diverticulum
(D) Tracheoesophageal septum
(E) Bronchopulmonary segment

7. Collapse of bronchi caused by failure of bronchial cartilage development is indicative of which one of the following congenital malformations?

(A) Congenital bronchial cysts
(B) Congenital neonatal emphysema
(C) Tracheoesophageal fistula
(D) Hyaline membrane disease
(E) Pulmonary hypoplasia

8. Pulmonary hypoplasia is commonly associated with which condition?

(A) Hyaline membrane disease
(B) Diaphragmatic hernia
(C) Tracheoesophageal fistula
(D) Congenital bronchial cysts
(E) Congenital neonatal emphysema

9. Development of which of the following is the first sign of respiratory system development?

(A) Tracheoesophageal septum
(B) Hypobranchial eminence
(C) Primitive foregut
(D) Tracheoesophageal fistula
(E) Respiratory diverticulum

10. In which stage of lung maturation is the blood–air barrier established?

(A) Embryonic period
(B) Pseudoglandular period
(C) Canalicular period
(D) Terminal sac period
(E) Alveolar period

Answers and Explanations

1. **B.** Tracheoesophageal fistula is an abnormal communication between the trachea and esophagus that results from an improper division of the foregut by the tracheoesophageal septum. It is generally associated with esophageal atresia and polyhydramnios.
2. **B.** Respiratory distress syndrome is common in premature infants and infants of diabetic mothers. It is caused by a deficiency or absence of surfactant. Collapsed alveoli and eosinophilic material consisting of fibrin (hyaline membrane) can be observed histologically, indicating associated hyaline membrane disease.
3. **B.** The epithelial lining of the entire respiratory system (from tracheal epithelium to type I pneumocytes lining alveoli) is derived from endoderm.
4. **D.** The epithelium of primary bronchi is derived from endoderm; the other components are derived from visceral mesoderm.
5. **E.** The blood–air barrier comprises the structures through which gaseous exchange occurs between air in alveoli and blood in pulmonary capillaries. The attenuated pulmonary epithelium (type I pneumocytes) is derived from endoderm. The simple, squamous epithelium (endothelium) lining pulmonary capillaries is derived from visceral mesoderm.
6. **D.** When the tracheoesophageal folds fuse in the midline, they form the tracheoesophageal septum. This septum is responsible for separating the adult trachea ventrally from the esophagus dorsally.
7. **B.** Congenital neonatal emphysema is a malformation involving the bronchi. One or more lobes of the lungs are overdistended with air because air can be inspired through collapsed bronchi but cannot be expired.
8. **B.** During normal development, a space is provided for the prolific growth of the bronchial buds in a lateral and caudal direction. This space, which is part of the intraembryonic coelom, is called the primitive pleural cavity. If this space is reduced by herniation of abdominal viscera, lung development will be severely compromised.
9. **E.** Development of the respiratory system begins in week 4; the first sign of development is formation of the respiratory diverticulum in the ventral wall of the primitive foregut.
10. **D.** The simple cuboidal epithelium within the terminal sacs differentiates into pneumocytes within the terminal sac period. The rapidly proliferating capillary network makes intimate contact with the terminal sacs, and the blood–air barrier is established with type I pneumocytes. These events take place in the terminal sac period, which runs from embryonic week 24 until birth.